SECTION II
REMARKS

Regarding the Amendments

Claims 1, 10, 20, and 24-27 have been amended as set forth in the above Complete Listing of the Claims.

As amended, the claims are supported by the specification and the original claims and do not add new matter, as defined by 35 U.S.C. § 132.

In particular, the amendment to claim 1 is supported by original claims 2 and 3.

The amendment to claim 10 has been made such that the claim properly depends from claim 1.

The amendments to claim 20 are supported by previously pending claims 24 and 31.

Claims 25-27 are amended to proper dependent form in light of the amendment of claims 20 and 24.

The amendments do not require a new search, or raise new issues for consideration because they merely address issues already raised by the examiner or define applicants' invention more clearly. It is submitted that the amendments place the claims in condition for allowance or in better condition for appeal by reducing the number of issues for consideration on appeal.

The amendments were not made earlier in the prosecution because it is maintained that the previously pending claims were allowable. Since the amendments do not add new matter or require a new search or consideration, and place the claims in condition for allowance or in better condition for appeal, entry of the amendment is respectfully requested.

By the present amendment, cancellation of claims 2, 3, 22, 28, and 31-35 is requested, without prejudice.

Thus, upon entry of the amendments, claims 1, 8, 10-15, 19, 20, 23-27, 29 and 30 will be pending.

Rejection of the Claims Under 35 U.S.C. §112, first paragraph – Enablement

In the Final Office Action mailed July 9, 2008, the examiner has maintained the rejection of

claims 1-3, 8, 10-15, 19, 20 and 22-29 under 35 U.S.C. §112, first paragraph as lacking enablement. Of the rejected claims, claims 2, 3, 22, and 28 have been cancelled by the present action. Applicants respectfully disagree with the rejection of presently pending claims 1, 8, 10-15, 19, 20, 23-27 and 29 under 35 U.S.C. §112, first paragraph.

A determination of enablement under 35 U.S.C. §112, first paragraph is based on an evaluation of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without "undue experimentation." Applicants assert that the claims of the present application are so enabled.

The claims of the invention recite a diagnostic conjugate comprising the following modules: 1) a transmembrane module, 2) an address module and 3) a signaling module. Each module element is further described in the independent and dependent claims.

On page 4 of the Final Action the Examiner has acknowledged that the specification is enabling for:

> A diagnostic conjugate for the molecular imaging of a human tumor expressing a c-myc, c-ras, hern, sst1 or sst2 gene comprising in sequential order:
> A transmembrane peptide of SEQ ID Nos. 2, 3 or 4, conjugated via a cleavable linker to the a [sic] peptide nucleic acid which hybridizes with a c-myc, c-ras, hern, sst1 or sst2 mRNA, conjugated via a linker to a $Gd3^+$ complex, wherein said target specific antisense conjugated $Gd3^+$ transporter complex is transported across the cell membrane, wherein a hybrid is formed of said an antisense peptide nucleic acid and the RNA target sequence, wherein said hybrid begins to be slowly enzymatically cleaved, thereby releasing the target specific antisense conjugated $Gd3^+$ transporter.

As such, the examiner has acknowledged the enablement of specific diagnostic conjugates. The examiner's attention is respectfully drawn to the amended claims, as set forth in Section I above.

With regard to the transmembrane module element, independent claims 1 and 20 recite transmembrane modules that are human transmembrane peptides comprising SEQ ID NO: 2, 3, or 4. Furthermore, the transmembrane modules are recited in independent claims 1 and 20 as linked to the antisense peptide nucleic acid via a spacer. The examiner's attention is respectfully drawn to the specification at page 6, the last full paragraph, where the spacer is described as eliminating or minimizing steric hindrances between the modules. In a preferred embodiment the

spacer may be cleavable but, contrary to the assertion of the Examiner on page 6, last paragraph of the Final Office Action, a cleavable spacer is not essential.

In the Office Action mailed April 2, 2007, the examiner cited U.S. Patent No. 6,821,948. In example 4 of that patent it is shown that a peptide nucleic acid antisense to c-myc coupled to a transport peptide (nuclear location sequence from 5V40-T antigen) via a non-cleavable polylysine spacer suppresses c-myc expression. Therefore, this example demonstrates that the polylysine spacer is sufficient to permit the peptide nucleic acid to hybridize with the c-myc target. Accordingly, it is not essential that a spacer between the human transmembrane peptide and the peptide nucleic acid be cleavable in order to use such a conjugate. The presently pending claims contain spacers that are not necessarily cleavable spacers. This subject matter is enabled. As demonstrated by the example cited above from U.S. Patent No. 6,821,948, no undue experimentation would be required for one of skill in the art to make and use a conjugate containing a spacer, as claimed.

With respect to the signaling module of the conjugate, the examiner alleges on page 7, last paragraph of the Final Office Action that "*it would require undue experimentation to make the broadly claimed compounds in order to minimize undesired interactions between the trapping Gd and the rest of the conjugate or to specifically penetrate the plasma membrane in a target cell because of the hydrophobicity of Gd chelates conjugates*", referring to p. 2295, col. 2, para. 1; p. 2344, col. 2 of Caravan et al. for support. The cited passages of Caravan et al. refer to compounds such as "Magnevist®" ($Gd(DTPA)(H_2O)^{2-}$) which is the signalling compound of the working example of the present application. Caravan et al. describe this compound as "a little hydrophilic ball" which is unlikely to enter cells (p. 2295, col.2, para.1) and belongs to the category of "more hydrophilic agents" (p.2344, col.2). Since this compound belongs to the more hydrophilic agents among the available Gd-compounds (see table 28), the resistance of this compound to enter into cells is higher than that of the other less hydrophilic compounds.

However, applicants have demonstrated in the present application that $Gd(DTPA)(H_2O)^{2-}$ can enter the target cell with the rest of the conjugate. Therefore, other compounds trapping Gd and having a similar low hydrophobicity as $Gd(DTPA)(H_2O)^{2-}$ or even a higher hydrophobicity will likewise enter the target cell, since compounds having higher hydrophobicity pass through the cell membrane much more easily than does $Gd(DTPA)(H_2O)^{2-}$. To avoid undesired interactions between the trapping Gd and the rest of the conjugate, a spacer is used to eliminate steric hindrances, as discussed above. Applicants therefore have provided the necessary showing that

Gd-trapping signalling modules enter the target cell together with the rest of the conjugate. Thus, no require undue experimentation is required for one of skill in the art to obtain the claimed conjugate.

Accordingly, pending claims 1, 8, 10-15, 19, 20, 23-27 and 29 are enabled and in compliance with the requirements of 35 U.S.C. §112, first paragraph. Withdrawal of the rejection is therefore respectfully requested.

Rejection of Claims 1 and 20 Under 35 U.S.C. §103

In the Final Office Action mailed July 9, 2008, the examiner has maintained the rejection of claims 1-3 and 15 over Braun et al. in view of Caravan et al. and has included claims 20, 30 and 31 in the rejection. Applicants respectfully disagree.

Initially, it is noted that claims 2, 3, and 31 have been cancelled by the present Response. Accordingly, the discussion below will discuss pending rejected claims 1, 15, 20 and 30.

The examiner's attention is respectfully drawn to the amended claims, as set forth in Section I above. By the present Response, the claims have been amended such that independent claims 1 and 20 (and therefore all claims dependent therefrom) include the element of a transmembrane module comprising SEQ ID NO: 2, 3, or 4. To support a rejection under 35 U.S.C. 103, the prior art reference(s) must teach all of the limitations of the claims. MPEP § 2143.03.

The combination of Braun et al. in view of Caravan et al. does not provide inclusion of a human transmembrane peptide, in particular one having SEQ ID NO: 2, 3 or 4.

Braun et al. include use of peptides derived from penetratin (*Drosophila*), transportan (synthetic galanin(1-12)-Lys-mastoparan (1-14) amide), viral transport proteins and bacterial transport peptides. However, Braun et al. describe a transport peptide of human origin, in particular not one having SEQ ID NO: 2, 3 or 4. Therefore, a person of ordinary skill in the art viewing conjugates in view of the provisions of Braun et al. would not have been motivated to make a conjugate having a human transmembrane peptide of SEQ ID NO: 2, 3 or 4, which minimizes the risk of immunizing reactions.

The subject matter of Caravan et al. does not remedy the deficiencies of Braun et al.

Braun et al. in view of Caravan et al. therefore fail to provide any derivative basis for the claimed invention. Accordingly, no basis of *prima facie* obviousness of the claimed invention is presented by such cited references.

The present invention provides a conjugate which allows for rapid accumulation of the gadolinium contrast agent in the cells and allows distinction between non-tumor and tumor cells due to the specific retention in tumor-cells. Such was not possible with the Gd-agents of the prior art. The present invention recites diagnostic conjugates for tumor imaging. It was not suggested in the prior art to use peptide nucleic acids for MRI. Example 2 of the present invention, however, demonstrates that such use is possible with the claimed conjugates.

Since Braun et al. in view of Caravan et al. does not provide any logical basis for the diagnostic conjugates for tumor imaging recited in independent claims 1 and 20 and claims 15 and 30 dependent therefrom, Braun et al. in view of Caravan et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1-3, 15, 20, 30 and 31 under 35 U.S.C. § 103 (a) as being obvious over Braun et al. in view of Caravan et al. is respectfully requested.

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CONCLUSION

All of Applicants' pending claims 1, 8, 10-15, 19, 20, 23-27, 29 and 30 are patentably distinguished over the art, and in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the July 9, 2008 Office Action without extension was set at three months, or October 9, 2008. This Response is therefore timely and no fees are believed to be due for the filing of this paper. However, should any fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the Examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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